Perioperative diclofenac application during video-assisted thoracic surgery pleurodesis modulates early inflammatory and fibrinolytic processes in an experimental model

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Original Paper

Perioperative Diclofenac Application during Video-Assisted Thoracic Surgery Pleurodesis Modulates Early Inflammatory and Fibrinolytic Processes in an Experimental Model

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Key Words
Adhesion · Cytokines · Fibrinolysis · Non-steroidal anti-inflammatory drugs · Pleurodesis

Abstract
Background/Purpose: It has been substantiated that the quality of pleurodesis is reduced when non-steroidal anti-inflammatory drugs (NSAIDs) are used perioperatively. The effects of NSAID administration on the early inflammatory and fibrinolytic processes after mechanical pleurodesis were investigated in an established pig model. ***Methods:*** Left-sided mechanical pleural abrasion was performed on 24 pigs assigned to either an NSAID or a control group. Pleural fluid and blood samples were analysed over a 24-hour period. Histological evaluation of neutrophil influx at the site of pleural abrasion was performed. ***Results:*** The volume of pleural effusion was significantly decreased in the diclofenac group at 10 and 24 h, and the protein content was significantly lower. The diclofenac group at 24 h had a diminished total number of white blood cells and a reduced content of transforming growth factor-β. Moreover, the diclofenac group had a reduced percentage of neutrophils at 6 h. Significantly increased levels of D-dimers and tissue plasminogen activator were measured at 6 h and of interleukin-10 at 24 h. Neutrophils at the site of pleural abrasion were significantly reduced. ***Conclusions:*** Systemic application of diclofenac led to a local enhancement of fibrinolysis and attenuation of pro-inflammatory and fibrotic processes necessary for adhesion formation in our model.

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Introduction

Video-assisted thoracic surgery (VATS) for mechanical pleurodesis is an established and reliable procedure for the treatment of recurrent spontaneous pneumothorax and of malignant pleural effusion. Non-steroidal anti-inflammatory drugs (NSAIDs) are being used with increasing frequency as systemic opioid-free analgesia due to their potent analgesic effects without having side effects on the central nervous system. It has been proven that the quality of adhesions formed 3 weeks after mechanical pleurodesis in a pig model is reduced when NSAIDs such as diclofenac are used perioperatively [1]. Similar findings were also described after talc or silver nitrate pleurodesis in different animal models [2]; nonetheless, to our best knowledge no multicentre trial has been assigned to assess these experimental observations. One hypothesis is that cyclo-oxygenase-2 (COX-2) inhibitors such as diclofenac inhibit the immediate postoperative inflammatory process necessary for pleural symphysis, due to their ability to suppress prostaglandin synthesis.

However, the exact mechanism by which NSAIDs affect collagen deposition and the time course of the events leading to the formation of fibrin and of adhesions after pleurodesis have not been completely elucidated. The process of adhesion formation after a mechanic or toxic injury leads to the production and release of pro- and anti-inflammatory mediators by the local mesothelial cells. Another essential process during adhesion formation is the activation of the coagulation cascade [3].

The aim of the underlying study was to clarify the following hypothesis: mediators of early pro- and anti-inflammatory as well as fibrinolytic processes are attenuated by perioperative diclofenac application in an established pig model of video-assisted thoracoscopic mechanical pleural abrasion.

Materials and Methods

Animals

All animals were kept in the facility of the University Hospital Zürich. They had free access to standard laboratory pig chow and water in a temperature-controlled room with a 12-hour light/12-hour dark cycle with at least 10 days' acclimation before experiments. The study was approved by our Institution's Committee on Investigations involving animal subjects with the reference No. 142/2003. Animal care was provided in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health NIH No. 86-23, revised, 1985) and in compliance with the European Convention on Animal Care.

Study Design

24 pigs (Schweizerisches veredeltes Landschwein) with a mean weight of 32.8 kg (range 29.2–36.4 kg) were randomly assigned to either a treatment group or a control group of 12 animals each. The experiments were performed in 2 series. All animals of the first series (n = 12) did not remain under anaesthesia and survived 24 h until autopsy. Based on the preliminary results of the first series, we expected that the most relevant events leading to adhesion formation happened earlier than 24 h. Therefore, we chose a total observation period of 10 h, and in agreement with the veterinarian office all animals of the second series (n = 12) were maintained under anaesthesia. Surgeons performing VATS pleural abrasion and pathologists analysing specimens were blinded to the treatment. In the NSAID treatment group, animals received 50 mg diclofenac (Voltaren®) orally twice a day beginning 2 days before the intervention until autopsy. A total of 12 out of 24 animals received postoperative analgesia with a patch of fentanyl 75 μg/h (Durogesic TTS® 75 μg/h). Gastric ulcer prophylaxis was applied with a selective blocker of the proton pump (omeprazole) 40 mg daily beginning 2 days before the operation. All drug dosages were the same as in our previous publication and correspond to the usual dosage in humans [1]. Narcosis and unilateral left-sided apical mechanical pleural abrasion were performed by the use of the VATS technique as previously described [1]. Pleural fluid (fluid recovered via a chest drainage) and blood

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samples were collected at different time points in each animal. After a lethal intracardiac potassium injection under deep narcosis, the chest wall was excised, fixed in 4% paraformaldehyde and assessed for histopathological examination.

Blood and Pleural Fluid Cytokine Determination

Blood samples were assessed 7 days before the operation, on the day of operation and 2, 4, 6, 8, 10, 17 and 24 h postoperatively throughout a central venous catheter placed at the beginning of the operation under narcosis by preparation and cannulation of the left external jugular vein.

The complete amount of the pleural fluid was harvested by aspiration via drainage at 6, 10 and 24 h postoperatively.

For serum and plasma collection, a serum separator tube was used to collect serum, and the samples were clotted for 60 min at room temperature. For plasma, we used a 0.129 mol/l Na citrate separator tube. All blood samples were then centrifuged at 3,280 rpm in an Eppendorf 5810 R table centrifuge for 10 min at 4°C. Serum or plasma supernatants were collected and transferred in 15-ml sterile tubes and centrifuged at 4,000 rpm as above. Samples were alliquoted in sterile tubes and either assayed immediately (human tissue plasmin activator) or plunged in liquid nitrogen and stored at ≤–80°C until use.

White blood cells with percentage of neutrophils, platelets and D-dimers were quantified at the Institute of Haematology from the University Hospital Zürich. Cytokine levels either in pleural fluid, serum or plasma according to the parameter were measured by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's protocols. The kits for porcine interleukin-1β (IL-1β), porcine interleukin-6 (IL-6), porcine interleukin-8 (IL-8), porcine interleukin-10 (IL-10) and porcine tumour necrosis factor-α (TNF-α) were Duoset ELISA kits (Duoset, R & D Systems, Minneapolis, Minn., USA). The porcine transforming growth factor-β_1 (isoform β_1, active form of TGF-β) was analysed with a Quantikine ELISA (Quantikine, R&D Systems). The human tissue plasminogen activator activity assay (tPA) was from Innovative Research (Southfield, Mich., USA).

Histopathological Assessment

Formalin-fixed chest walls were decalcified with EDTA and stained with haematoxylin-eosin and elastin-van Gieson in predefined areas of pleural abrasion. A semiquantitative analysis of the neutrophil granulocytes in the pleura was assessed by a pathologist blinded to the treatment (P.V.) with the following semiquantitative score: 0 = no infiltration; 1 = scattered foci with some neutrophil granulocytes; 2 = several granulocytes; 3 = dense infiltration of granulocytes.

Statistical Analysis

Sample size calculation was computed with the Windows program 'nQuery Advisor' Elasthoff, 1995. Statistical analysis was conducted using the SPSS software package for Windows (version 18.0; SPSS Inc., Chicago, Ill., USA). Data are expressed as means and standard deviations. Data were natural logarithm transformed if necessary to reach approximate normality. Non-parametric data are expressed as medians and 25–75% interquartile intervals. A repeated-measures analysis of variance was applied to test for a difference between the groups (characterized by the between-subjects effect) over the whole period of measurements. Student's t tests were performed when data were normally distributed as post-hoc tests to compare both groups at some time points. A non-parametric analysis of variance (Mann-Whitney test) was applied for histological analysis. The data were expressed as medians ± SD. p values smaller than 0.05 were considered to be significant.

Results

Analysis of the Pleural Fluid Parameters

The anti-inflammatory cytokine IL-10 was significantly increased after 10 h (31.41 ± 3.17 pg/ml) in the NSAID group in comparison to 26.43 ± 1.8 pg/ml in the control group ($p \leq 0.05$; table 1; fig. 1). The active fibrosis-inducing cytokine TGF-β_1 24 h after pleural abrasion was significantly decreased in animals treated with the NSAID (1.99 ± 0.38 pg/ml) compared with the control group (2.99 ± 0.64 pg/ml; $p \leq 0.01$; table 1; fig. 2). For the

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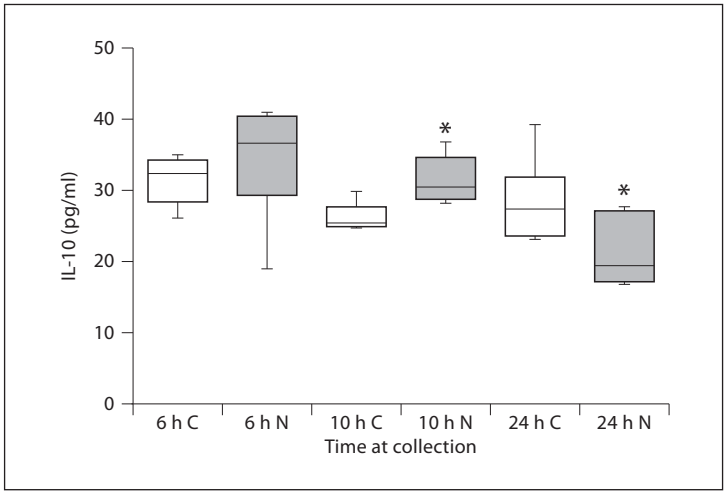

Fig. 1. Box plots of IL-10 levels in the pleural fluid measured at different time points. * $p \leq 0.05$. N = NSAID group; C = control group.

Table 1. Comparison of pleural fluid after mechanical pleurodesis with and without diclofenac

	6 h		10 h		24 h	
	control	NSAID	control	NSAID	control	NSAID
Cytokine and fibrinolysis parameters						
IL-1β, ng/ml	2.16 ± 0.73	2.01 ± 0.99	2.47 ± 0.36	2.46 ± 0.41	1.63 ± 0.90	1.24 ± 0.63
IL-6, ng/ml	4.39 ± 0.35	4.13 ± 0.48	4.45 ± 0.19	4.10 ± 0.37	4.07 ± 0.41	3.19 ± 1.27
IL-8, ng/ml	0.73 ± 0.61	0.88 ± 0.55	0.80 ± 0.86	0.61 ± 0.39	0.15 ± 0.21	0.13 ± 0.22
TNF-α, pg/ml	98.84 ± 13.30	106.83 ± 23.75	83.06 ± 14.29	92.05 ± 13.04	91.57 ± 21.05	84.23 ± 24.15
IL-10, pg/ml	31.48 ± 3.25	34.26 ± 8.19	26.43 ± 1.8	31.41 ± 3.17[b]	28.4 ± 5.86	21.27 ± 4.66[b]
TGF-β_1, pg/ml	3.33 ± 1.55	3.34 ± 2.83	4.54 ± 1.54	4.18 ± 2.83	2.99 ± 0.64	1.99 ± 0.38[b]
D-dimers, mg/ml	5.24 ± 1.03	11.64 ± 6.34[b]	4.15 ± 1.18	6.68 ± 3.03	4.85 ± 1.14	4.81 ± 0.60
tPA, fg/ml	193.3 ± 37	381.7 ± 186[b]	225.0 ± 38.1	403.3 ± 230	70.4 ± 58	87.1 ± 51
Pleural secretion parameters						
Volume, ml	16.33 ± 5.64	20 ± 25.3	21.83 ± 10.38	9.33 ± 6.68[a]	67.5 ± 3.53	1.5 ± 0.70[a]
Cells/μl	18,680 ± 7,738	14,800 ± 9,219	25,700 ± 21,113	8,425 ± 4,349	20,420 ± 9,144	7,850 ± 2,268[a]
Neutrophils, %	87 ± 4.3	64 ± 11[b]	75.5 ± 30.35	63.5 ± 25.47	82.66 ± 10.19	69.66 ± 33.52
Total protein, g/l	29.83 ± 2.31	28.66 ± 1.52	33.33 ± 2.87	18.5 ± 11.35[a]	36.5 ± 2.12	28.75 ± 0.35[a]

All data are means ± standard deviation. [a] $p \leq 0.05$: comparisons of parameters; [b] $p \leq 0.05$: comparisons of natural-logarithm-transformed parameters.

fibrinolysis parameters, a significant increase in the fibrinolytic marker D-dimer was measured at 6 h in the NSAID group (11.64 ± 6.34 mg/ml) in comparison to the control (5.24 ± 1.03 mg/ml; $p \leq 0.05$; table 1). For the cellular and biochemical parameters of the pleural fluid, NSAID treatment triggered a significant reduction in total cell numbers at 24 h (7,850 ± 2,268 cells/μl) when compared to the control group (20,420 ± 9,144 cells/μl; $p \leq 0.01$; table 1). The percentage of neutrophils after NSAID treatment was also reduced (64 ± 11%) in comparison to control (87 ± 4.3%; $p \leq 0.01$; table 1; fig. 3) and this already 6 h after pleural abrasion. The volumes of pleural effusion collected in the NSAID groups at 10 h (9.33 ± 6.68 ml) and 24 h (1.5 ± 0.7 ml) were significantly lowered as compared with the control groups (21.83 ± 10.38 ml, $p \leq 0.03$, and 67.5 ± 3.53 ml, $p \leq 0.01$, respectively; table 1). Furthermore, the total level of protein decreased in the

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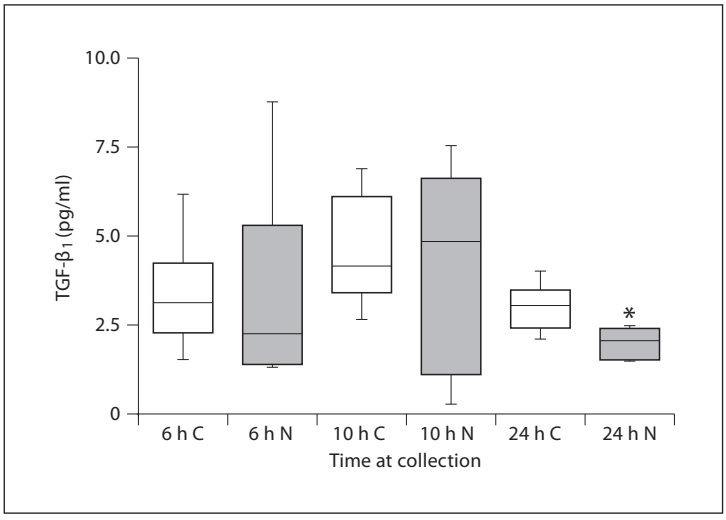

Fig. 2. Box plots of active TGF-β_1 levels in the pleural fluid measured at different time points. * $p \leq 0.05$. N = NSAID group; C = control group.

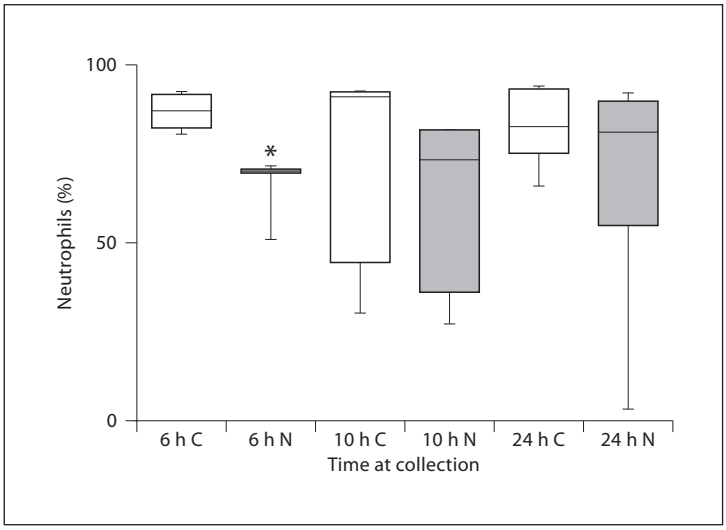

Fig. 3. Box plots of neutrophil levels in the pleural fluid measured at different time points. * $p \leq 0.05$. N = NSAID group; C = control group.

NSAID groups at both time points of 10 h (18.5 ± 11.35 g/l) and 24 h (28.75 ± 0.35 g/l) as compared with the control groups (33.33 ± 2.87 g/l, $p \leq 0.01$, and 36.5 ± 2.12 g/l, $p \leq 0.04$, respectively; table 1).

We found only a small non-significant trend of the pro-inflammatory cytokines IL-1β and IL-6 and the chemokine IL-8 to be reduced after NSAID treatment (table 1).

Analysis of the Blood Parameters

The anti-inflammatory cytokine IL-10 increased quickly until 6 h after pleural abrasion and levels were always higher in the NSAID group but not significantly in comparison to the control (not shown). Although TGF-β levels decreased from the time of operation until autopsy, evolution and comparison with the control group were not significant. The fibrinolysis parameter tPA exhibited a maximum plasma level 4 h after pleural abrasion in NSAID-treated animals and was higher although not significantly different when compared with controls. Plasma levels of D-dimer in NSAID-treated animals significantly increased over

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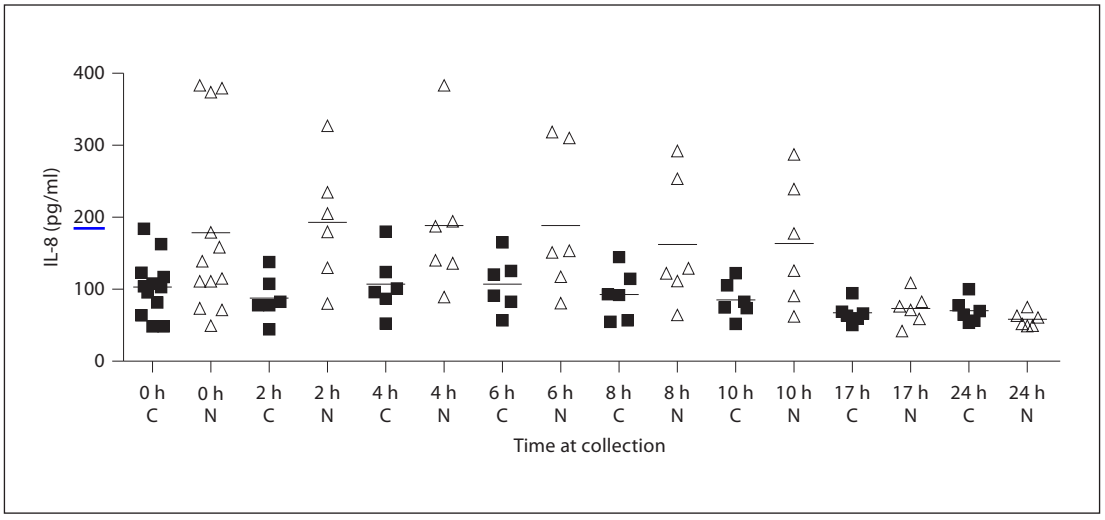

Fig. 4. Scatter plots of IL-8 levels in the blood measured at different time points. N = NSAID group; C = control group.

time ($p \leq 0.01$), reached their maximum after 17 h, but the difference to the control group was not statistically significant.

The pro-inflammatory chemokine IL-8 was significantly increased in the serum of the NSAID group during the first 10 h from a mean value of 192 ± 35 pg/ml (2 h) to 151 ± 35 pg/ml (10 h; $p \leq 0.03$; fig. 4). Since IL-8 induces chemotaxis of neutrophils, a permanently higher level of neutrophils in the serum was also measured over the first 10 h in the NSAID group in comparison to the control group (not shown). Nonetheless, this initial difference in the dynamics of IL-8 production during the first 10 h could not be significantly established comparing the two groups. The pro-inflammatory cytokines TNF-α, IL-6 and IL-1β did not significantly differ between both groups, although IL-6 and IL-1β levels were always lower in the group treated with the NSAID (not shown).

We did not detect significant differences between all blood parameters measured in the NSAID or the control groups 7 days before the day of operation.

Histopathological Analysis

Histological analysis after haematoxylin-eosin staining of the sites of pleural abrasion exhibited in the NSAID-treated group showed a significantly reduced number of neutrophils in comparison with the control group. The score value for the NSAID-treated group was 3.0 ± 0.44 versus 1.0 ± 0.44 in the control group ($p \leq 0.01$; fig. 5a, b).

Discussion

The results of the study suggest that perioperative diclofenac application during VATS pleurodesis leads to modulations in anti- and pro-inflammatory as well as fibrinolytic processes during the first 24 h or early postoperative phase and confirm our previous observations of reduced adhesion 15 days after surgery [1].

Diclofenac is considered a non-selective COX inhibitor but published evidence suggests that it is a predominant COX-2-inhibitor [4] and modulates arachidonic acid levels in a variety

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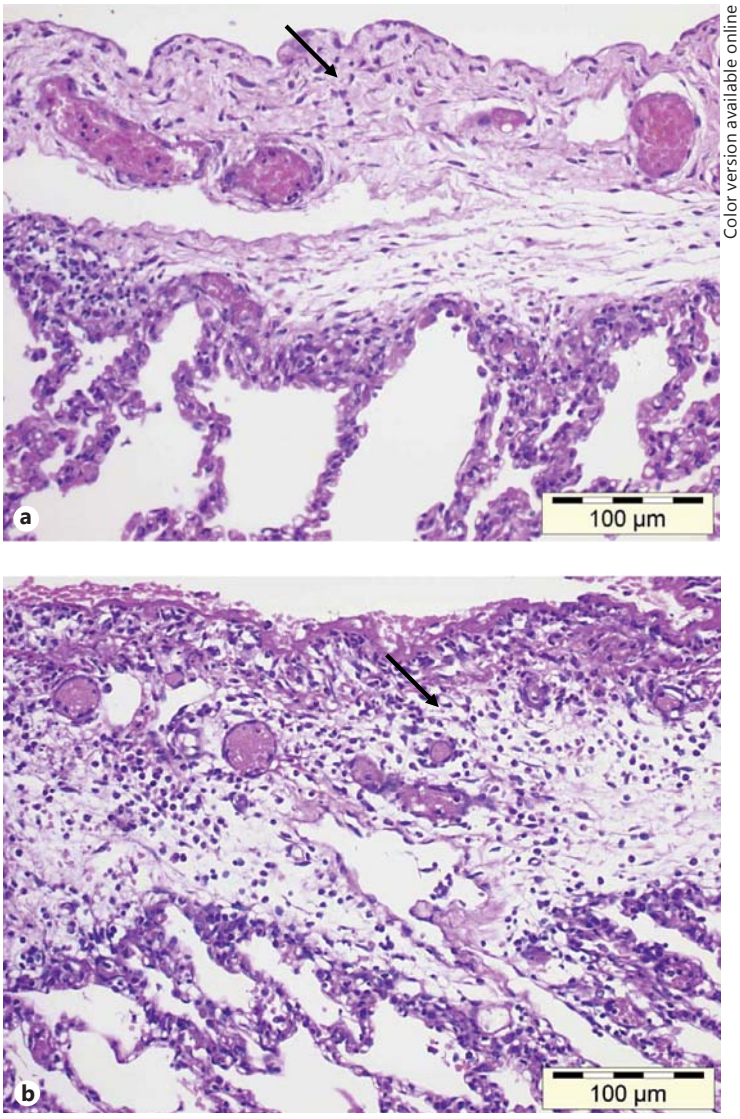

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Fig. 5. a, **b** Representative haematoxylin-eosin stainings of animals treated with NSAID (score 0; **a**, with only rare neutrophils in the tissue) in comparison to control (score 3; **b**, with dense neutrophil infiltration in the tissue, arrows).

of tissues. Arachidonic acid metabolites are synthesized by the cells present at the site of inflammation and mediate many aspects of postsurgical inflammation. As a result of personal observation by our group and others, the perioperative use of NSAIDs during pneumothorax intervention was abandoned [1]. The results of our previous experiments confirmed our suspicion [1] and led us to assess, in the same model, the impact of the early postoperative processes. There is good evidence on the experimental level that the process of adhesion is hampered by the use of NSAIDs [5, 6]. In a rabbit model, Liao et al. [7] could establish that short-term administration of ketoprofen, a relative selective COX-1 inhibitor, does not decrease the effect of talc pleurodesis.

In order to achieve a good pleurodesis for the treatment of pneumothorax and pleural effusion, an essential step is the appropriate release of mediators for inflammation and fibrosis produced by mesothelial cells. The panel of pro-inflammatory (IL-1, IL-6, IL-8 and TNF-α) and anti-inflammatory cytokines (IL-10) we have chosen for analysis are liberated during the process of adhesion formation and induce further processes themselves such as

neutrophil activation by the chemokine IL-8 [8]. Another essential mechanism during adhesion formation is the balance between the activation of the coagulation cascade and the fibrinolysis represented by tPA [3].

The reduction of total protein in the pleural fluid is probably due to the fact that secretion of inflammatory proteins such as TGF-β, IL-6 and IL-1β is altered; a general trend of decrease in these proteins although insignificant – besides TGF-β – was described after NSAID treatment. Apart from this, TGF-β is known to be a potent inducer of pleurodesis [9], and elevated pleural fluid levels were measured in a rabbit model after talc pleurodesis [10]. In our study, TGF-β was significantly reduced in the pleural fluid after mechanical pleurodesis and simultaneous treatment with diclofenac.

In adhesion formation, TGF-β activates plasminogen activator inhibitor [11], and it interacts in its active form with the fibrinolytic system. Demonstration of failed talc pleurodesis was associated with increased pleural fibrinolysis [12]. Therefore, in the presence of diclofenac, both reduced levels of TGF-β and increased levels of fibrinolysis factor D-dimer and human tPA in the pleural fluid may explain the reduced effect on pleurodesis described 3 weeks after thoracoscopic pleural abrasion [1].

IL-8 has been shown to be an important chemokine in the development of acute pleural inflammation [10] specifically as a chemotactic agent for neutrophils [13, 14]. In our study we measured elevated IL-8 levels in the serum of diclofenac-treated animals and observed a trend for high neutrophil levels in the blood. Diclofenac is well described as an agent which induces L-selectin (CD62L) shedding from human neutrophils, and potentially reduces the extravasation of these cells in tissue [15–17]. Moreover COX-2 inhibitors have been described to increase the levels of IL-8 by Wang et al. [18]. In our case, the neutrophils recruited did not migrate properly to the inflamed pleural abrasion site. A high level of IL-8 chemokine in blood and an increased cleavage of L-selectin on neutrophils might have maintained the neutrophils in the blood stream. This limited local inflammatory response is also reflected by a significantly lower total cell number and lower percentage of neutrophils in the pleural fluid of diclofenac-treated animals. Additionally the histopathologically examined neutrophil influx at the site of pleural abrasion was significantly reduced.

Although similarly altered anti-inflammatory and fibrinolytic processes present in the pleural fluid were also monitored in the blood, they were only for IL-8 levels significantly different between the groups. High levels of neutrophils in both blood (for NSAID-treated animals) and pleural fluid (for control animals) were generally associated with high levels of IL-8.

We should also report some potential limitations of this study. Since the pig-specific ELISA kits were often near the detection limit declared by the manufacturer in the blood, this might be one reason why we could not measure significant differences in cytokine concentrations between the two groups. Another potential limitation might be a certain heterogeneity between the animals of the 2 series. Since diclofenac induces also dose-dependent fluctuations of systemic cytokine levels, we should point out that the reported effects of diclofenac are also heterogeneous [19–22]. This was particularly well documented for TNF-α levels where elevation is described after diclofenac treatment but is partially abolished in a dosage of 3 mg/kg body weight s.c. [23]. These problems may be clarified in an epidemiological trial evaluating the rate of recurrence after mechanical pleurodesis and the use of NSAIDs [24].

In conclusion, we validated that systemic application of diclofenac led to a local enhancement of fibrinolysis and attenuation of pro-inflammatory and fibrotic processes necessary for adhesion formation in an established pig model. These findings may explain the decreased success rate of pleurodesis after perioperative diclofenac treatment. In clinical practice, we currently avoid the use of diclofenac as perioperative pain man-

agement. Eventually, the use of COX-1 inhibitors such as ketoprofen according to the results of Liao et al. [7] may be a solution for perioperative analgesia after pleurodesis operations.

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